

## Original Research Article

# Prevalence and risk factors of hyperpigmentation induced by hydroxychloroquine in lupus patients

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### ABSTRACT

**Background:** Antimalarials including hydroxychloroquine (HCQ) have been used in the treatment of systemic lupus erythematosus (SLE) for more than 50 years. Few cases of hyperpigmentation attributed to HCQ have been reported in the literature from different geographical areas. However, no case reports or local studies from Saudi Arabia estimated the magnitude of HCQ adverse effect. This study aimed to estimate the prevalence of HCQ-induced hyperpigmentation and to investigate the possible risk factors related to this condition.

**Methods:** This retrospective study was conducted at King Abdulaziz University Hospital. All SLE patients on HCQ treatment, aged 18 years or above who visited Rheumatology and Dermatology Clinics were included. Those with the previous history of hyperpigmentation before starting HCQ treatment, or on chloroquine or quinacrine therapy were excluded. Medical records from September 2005 until June 2016 were reviewed.

**Results:** Out of 199 cases, 98 (49.2%) cases had hyperpigmentation, only 13 (13.3%) cases reported resolution. The main sites affected were the hands 46 (23.1%), followed by face 45 (22.6%), then feet 18 (9.0%), leg and whole body equally 12 (6.0%). There was a significant association between hyperpigmentation and receiving medications, history of ecchymosis, sun exposure, the presence of mucous membrane pigmentations ( $p < 0.0001$ ,  $p = 0.012$ ,  $p < 0.0001$ ,  $p = 0.022$  respectively).

**Conclusions:** HCQ-induced pigmentation is considered uncommon adverse effect of HCQ, with a prevalence rate of 49.2% indicated in this study. Furthermore, history of bruising, sun exposure, and the presence of mucous membrane pigmentation are possible predisposing factors.

**Keywords:** Hydroxychloroquine, Skin, Pigmentation, Systemic lupus erythematosus, Prevalence, Risk factors, Saudi Arabia

### INTRODUCTION

Systemic lupus erythematosus (SLE) is a prototypic multisystem autoimmune disease that affects 1 in 1000 individuals, most frequently women in their child-bearing years.<sup>1</sup> Antimalarials including hydroxychloroquine (HCQ) have been used in the treatment of SLE for more than 50 years. However, the broad spectrum of beneficial effects of these drugs in SLE has been demonstrated only in recent years.<sup>2</sup> Most experts now recommend lifelong hydroxychloroquine treatment in all SLE patients

regardless of disease severity or other therapy, if no contraindications exist.<sup>3</sup> Hydroxychloroquine has been reported to cause gastrointestinal, ophthalmological, neuromuscular, cardiac, hematological, and cutaneous side effects. Cutaneous side effects include hyperpigmentation, vitiligo, pruritus, psoriasis exacerbation, and hypersensitivity skin eruption.<sup>4</sup>

Ten to twenty percent of patients on long-term antimalarial therapy develop blue-grey skin pigmentation, typically on the face, hard palate, forearms, and shins.

This abnormal pigmentation is not always reversible with cessation of treatment.<sup>5</sup> Bleaching of the hair and transverse bands on the nail beds may also occur.<sup>6</sup> The factual biochemical basis for the pigmentation is unknown; it has been suggested that HCQ has an affinity for melatonin and concentrates in the skin. The binding of drug molecules to melatonin may cause a blue-black discoloration of the skin in patients treated with them for prolonged periods. These mucocutaneous hyperpigmentation were thought to be dose-dependent.<sup>7</sup> Only a few cases of hyperpigmentation attributed to HCQ have been reported in the literature from different geographical areas.<sup>8-11</sup> To our knowledge, no case reports or local studies from Saudi Arabia estimated the magnitude of HCQ adverse effect. Therefore, this study aimed to assess the prevalence of HCQ-induced hyperpigmentation and to investigate possible risk factors.

## METHODS

### Study design and eligibility criteria

This retrospective study was conducted in King Abdul-Aziz University Hospital, Saudi Arabia. All SLE patients on HCQ treatment, aged 18 years or above who visited Rheumatology and Dermatology Clinics were included. Those with previous history of hyperpigmentation prior to starting HCQ, or on chloroquine or quinacrine were excluded.

### Data collection

Medical records from September 2005 till June 2016 were reviewed. SLE was diagnosed according to the American College of Rheumatology Classification criteria. All patients' data were recorded including age, sex, race, skin type, other comorbidities, site of hyperpigmentation, medications used at onset, dose of HCQ, time of start of the drug, duration of treatment, time of appearance of hyperpigmentation, area affected whether sun exposed or not, mucus membrane or nail affection, time of resolution of hyperpigmentation upon withdrawal of drug, history of ecchymosis, sun exposure, any previous skin illness. In addition, all laboratory investigations were collected including complete blood count (CBC), coagulation profile, chemistry panel (kidney function, liver function, electrolytes, blood sugar, cholesterol and triglyceride), erythrocyte sedimentation Rate (ESR), C-reactive protein (CRP), complement, ANA, anti-dsDNA, anti-Ro(SSA)/anti-La(SSB), antiphospholipid antibodies (APLs).

### Data analysis

All data were analysed using the Statistical Package for the Social Sciences version 20. Categorical data were presented as numbers and percentages. Numerical data were tested for distribution and were presented as median and interquartile ranges. Chi -Square test was used to test

distribution of categorical variables. Statistical significance was accepted when P value is less than 0.05.

### Ethical considerations

The study got an ethical approval from the Institutional Review Board of King Abdulaziz University Hospital, Jeddah city, Kingdom of Saudi Arabia. Confidentiality of the collected data and participant's privacy were assured, and the data were used only for research purpose.

## RESULTS

Out of 199 cases, the majority were female 191 (96.0%) and only 8 (4.0%) were male. With median age score 35 years, and median weight score 63.8 Kg.

More than half 107 (53.8%) had chronic illness, where the main diseases were HTN 50 (25.1%), followed by renal diseases 44 (22.1%), then hypothyroidism 37 (18.6%), dyslipidemia 20 (10.1%), DM 17 (8.5%), and lastly 4 (2.0%). About 26% of the patients received HCQ alone while 24% of the cases received HCQ in combination with other drugs (Table 1).

**Table 1: Medical characteristics.**

Variables	N	%
<b>Skin type</b>		
Fair	1	0.5
Medium	25	12.6
Olive	82	41.2
Brown	71	35.7
Black	20	10.1
<b>Co -morbidity</b>		
No	92	46.2
Yes	107	53.8
<b>Chronic illness #</b>		
HTN	50	25.1
Renal diseases	44	22.1
Hypothyroidism	37	18.6
DM	17	8.5
Dyslipidemia	20	10.1
Liver diseases	4	2.0
<b>Medication</b>		
No Medications	74	37.2
Cortisone	10	5.0
HCQ	52	26.1
Cortisone and HCQ	35	17.6
Cortisone, HCQ and others	8	4.0
HCQ and others	5	2.5
Others	15	7.5

Out of 199 cases, 98 (49.2%) cases had hyper pigmentation, only 13 (13.3%) cases reported resolution. Less than third 49 (25.1%) reported history of skin diseases, 60 (30.5%) reported history of sun exposure. Less than half 91 (45.7%) reported history of ecchymosis.

Less than third 51 (29.6%) reported other skin rash. Fourth of cases 48 (24.1%) reported that none sun exposed area was affected, and 33 (16.6%) reported that none sun exposed area was affected. The main sites affected were hand 46 (23.1%), followed by face 45

(22.6%), then feet 18 (9.0%), leg and whole body equally 12 (6.0%). The median scores were 5 years for “time of start of drug”, 3 years for “duration of treatment”, 3 years for “time of appearance of hyper-pigmentation”, and 200 for HCQ dose (Table 2).

**Table 2: Pigmentation patterns.**

Variables	N	%
<b>Hyper pigmentation</b>		
No	101	50.8
Yes	98	49.2
<b>Resolution (n=98)</b>		
Not applicable	66	67.3
No resolution	19	19.4
Resolution	13	13.3
<b>Hx of skin illness</b>		
No	149	74.9
Yes	49	25.1
<b>Hx of sun exposure</b>		
No	139	69.8
Yes	60	30.2
<b>Hx of ecchymosis</b>		
No	107	53.8
Yes	91	45.7
<b>Site</b>		
Not applicable	47	23.6
Face	45	22.6
Hand	46	23.1
Leg	12	6.0
Finger	2	1.0
Back	6	3.0
Feet	18	9.0
Knee	2	1.0
Neck	8	4.0
Whole body	12	6.0
others	23	11.6
<b>Area affected</b>		
None	108	54.3
None sun exposed area	48	24.1
Sun exposed area	33	16.6
<b>Any other skin rash excluding hyper-pigmentation</b>		
No	140	70.4
Yes	51	29.6
<b>Variables</b>		
	<b>Median</b>	<b>Quartile (25-75)</b>
Time of start of drug	5.0	(2 – 9)
Duration of treatment	3.0	(3 – 15)
Dose of HCQ	200	(200-400)

**Table 3: Laboratory investigations.**

Variables	N	%
<b>CBC</b>		
Low Hemoglobin	120	60.3
Normal Hemoglobin and Platelet	69	34.7
Low Platelet	10	5.0

Continued.

Variables	N	%
<b>Coagulation profile</b>		
Normal	127	63.8
Not found	47	23.6
High PTT and PT	13	6.5
Low PTT and PTT	7	3.5
Normal PT and Hight PTT	1	.5
Low PTT and normal PT	4	2.0
<b>Liver</b>		
Normal liver enzymes	109	54.8
High AST and ALT	8	4.0
High GGT and bilirubin	6	3.0
High bilirubin	2	1.0
High ALP	5	2.5
Low albumin	69	34.7
<b>Kidney</b>		
Normal kidney function	176	88.5
Not found	3	1.5
High urea and creatinine	20	10.0
<b>Blood sugar</b>		
Normal	92	46.2
Not found	80	40.2
High	27	13.6
<b>Chol/ TG</b>		
Normal	118	59.3
Not found	47	23.6
High TG and cholesterol	34	17.1
<b>ESR</b>		
Normal	53	26.6
Not found	11	5.5
High	135	67.8
<b>CRP</b>		
Normal	59	29.6
Not found	7	3.5
High	133	66.9
<b>C3_C4</b>		
Normal C3 and C4	73	36.7
Not found	7	3.5
High C3 and C4	56	28.1
Low C3 and C4	54	27.1
Low C3 and normal C4	8	4.0
Low C4 and normal C3	1	.5
<b>ANA</b>		
Not found	2	1.0
Negative: $\leq 1$ U	2	1.0
Strong positive: $\geq 6.0$ U	105	52.8
Positive: 3.0-5.9 U	65	32.6
Weak positive: 1.1-2.9 U	25	12.6
<b>ANTI_DNA</b>		
Normal	46	23.1
Not found	14	7.0
High	139	69.8
<b>SSA_SSB</b>		
Normal	3	1.5
Not found	125	62.8
Positive SSA	23	11.6
Negative	47	23.6
Borderline	1	0.5

Continued.

Variables	N	%
<b>APLs</b>		
Normal	1	.5
Not found	173	86.9
Positive	3	1.5
Negative	22	11.1
<b>ANTI_SM</b>		
Normal	3	1.5
Not found	138	69.3
Positive	10	5.0
Negative	47	23.6
Borderline	1	.5
<b>VITD</b>		
Normal	48	24.1
Not found	16	8.0
High	131	65.8

**Table 4: Pigmentation and associated factors.**

variables	Hyper pigmentation		P value	
	No	Yes		
	N (%)	N (%)		
<b>Skin type</b>	Fair	0 (0.0)	1 (1.0)	0.078
	Medium	16 (15.8)	9 (9.2)	
	Olive	46 (45.5)	36 (36.7)	
	Brown	30 (29.7)	41 (41.8)	
	Black	9 (8.9)	11 (11.2)	
<b>Gender</b>	Female	98 (97.0)	93 (94.9)	0.344
	Male	3 (3.0)	5 (5.1)	
<b>Chronic illness</b>	No	79 (78.2)	70 (71.4)	0.174
	Yes	22 (21.8)	28 (28.6)	
<b>Receiving medications</b>	No	51 (53.7)	23 (23.5)	0.0001*
	Yes	44 (46.3)	75 (76.5)	
<b>Hx of skin illness</b>	No	76 (75.2)	75 (77.3)	0.431
	Yes	25 (24.8)	22 (22.7)	
<b>Any other skin rash excluding hyper-pigmentation</b>	No	75 (76.5)	64 (66.7)	0.086
	Yes	23 (23.5)	32 (33.3)	
<b>Hx of sun</b>	No	74 (73.3)	65 (66.3)	0.181
	Yes	27 (26.7)	33 (33.7)	
<b>Hx of ecchymosis</b>	No	44 (45.4)	63 (62.4)	0.012*
	Yes	53 (54.6)	38 (37.6)	
<b>Area affected</b>	None	87 (95.6)	21 (21.4)	0.0001*
	None sun exposed area	4 (4.4)	44 (44.9)	
	Sun exposed area	0 (0.0)	33 (33.7)	
<b>Mucous membrane</b>	Normal	97 (96.0)	84 (85.7)	0.022*
	Presence of pigmentation	4 (4.0)	14 (14.3)	
<b>Presence of nail pigmentation (melanonychia)</b>	No	95 (94.0)	85 (86.7)	0.129
	Yes	6 (6.0)	13 (13.3)	

Laboratory characteristics for the patients are showed in Table 3. The results in Table 3 revealed a significant association between hyper pigmentation and receiving

medications, Hx of ecchymosis, area affected, mucous membrane, (p<0.0001, p=0.012, p<0.0001, p=0.022) respectively. On the other hand, there was no significant

association between hyper pigmentation and other factors (Table 4).

## DISCUSSION

In the present study, the prevalence of hydroxychloroquine-induced hyperpigmentation among lupus patients was 49.2%. Compared to our findings, the reported incidence of hydroxychloroquine-induced hyperpigmentation in patients with systemic lupus erythematosus was about 7%.<sup>12</sup> Moreover, Skare et al said that hydroxychloroquine was responsible for 33.0% of drug-related hyperpigmentation.<sup>4</sup> Recently, Bahloul et al reported the prevalence rate of 29% after accurate diagnosis of HCQ-induced pigmentations based on systematic dermatological examination.<sup>13</sup> Maubec et al had said that drug-induced pigmentation promoted in patients who are of prototypes V or VI, which is patients whose skin contain more melanin.<sup>14</sup> Therefore, might explain the high frequency of HQ-induced pigmentation in our study.

Among patients with hydroxychloroquine-associated hyperpigmentation, 13 cases (13.3%) reported resolution. It was known that hydroxychloroquine-related pigmentation slowly fades after discontinuation of the drug, and the indicated time for spontaneous decision is 2 to 6 months.<sup>4</sup> Additionally, Coulombe and Boccara reported cases of hydroxychloroquine associated hyperpigmentation where the skin discoloration was partially resolved four months after switching to chloroquine.<sup>15</sup> However, Morrison et al observed persistent hyperpigmentation one year after stopping the drug.<sup>16</sup> In contrast to this observation, Bahloul et al reported an improvement in pigmented lesions in 6 out of 22 patients with hydroxychloroquine-induced hyperpigmentation despite the maintenance of their daily dose of HCQ.<sup>13</sup>

Skin pigmentation related to antimalarial therapy presents clinically as yellow-brown to slate gray or black pigmentation, which commonly affects the anterior side of the shins, the face, forearms, mouth mucosa, and nail beds.<sup>13</sup> In contrast, skin pigmentations detected in our study were distributed mainly in the hands followed by the face, and then the feet and less frequently affected the legs. However, different pigmentation patterns were described.<sup>15,17</sup>

In the current study, skin pigmentations appeared after a median duration of HCQ treatment of 3 years with a median cumulative HCQ dose of 200. In comparison, Bahloul et al described HCQ-induced pigmentations after a median duration of HCQ treatment of 6.1 years with a median cumulative dose of 720 g.<sup>13</sup> However, Melikoglu et al presented a case of HCQ-induced skin pigmentations one year after starting the treatment.<sup>18</sup>

The mechanism for hyperpigmentation is poorly understood. In this study, there was a significant

association between hyperpigmentation and receiving medications, history of ecchymosis, sun exposure, and the presence of mucous membrane pigmentation. On the other hand, skin type, gender, chronic illness, history of skin illness or rash, or the appearance of nail pigmentation was not significantly related to the development of pigmentations. Comparable to our findings, Jallouli et al found that bruising, corticosteroid use, oral anticoagulants, antiplatelet agents, antiphospholipid syndrome and skin trauma were independent risk factors for hyperpigmentation.<sup>12</sup> Moreover, they identified that 22 patients (92%) reported that the appearance of pigmented lesions was preceded by the occurrence of ecchymotic areas, which gave way to a localized bluish-green or brown pigmentation that persisted for an unusually long time. Also, at the onset of pigmented lesions, 23 patients (96%) had at least one condition predisposing them to easy bruising, essentially treatment with oral anticoagulants and antiplatelet agents. Hence, they supported the hypothesis that HCQ-induced pigmentation first induced by ecchymosis or bruising. Likewise, recently, Bahloul and colleagues concluded a significant correlation between HCQ-induced pigmentation and the use of oral anticoagulants and antiplatelet agents.<sup>13</sup> Besides, they did not find gender differences between patients with or without pigmentations.

There is controversy regarding the nature of these pigmentations. Puri et al observed microscopic granules in the dermis that stained positive for melanin only.<sup>19</sup> However, consistent with the role of ecchymosis in the development of hyperpigmentation, skin biopsy from the pigmented areas revealed melanin granules and hemosiderin deposits within the dermis.<sup>20</sup> In addition, Bahloul and colleagues detected for the first time 10-fold increase in iron level in the pigmented lesions compared to healthy skin.<sup>13</sup>

Distribution patterns consistent with sun-exposed areas as reported in 33.7% of our patients may be attributed to phototoxic and photoallergic reactions with decreased minimal erythema dose due to HCQ.<sup>21</sup>

The limitations of our study are mainly due to its retrospective nature. Further prospective and studies that are more extensive were needed to precisely determine the incidence and risk factors of HCQ-induced pigmentation.

HCQ-induced pigmentation is considered uncommon adverse effect of HCQ, with a prevalence rate of 49.2% indicated in this study. Furthermore, history of bruising, sun exposure, and the presence of mucous membrane pigmentation are possible predisposing factors.

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